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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,182	BANKS, WILLIAM A.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-76* is/are pending in the application.

4a) Of the above claim(s) *6-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-76* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 20 October 2005 and 17 February 2006 have been entered.

Election/Restrictions

3. Claims 6 – 76 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1 March 2005.

New Rejections and Objections

Claim Objections

4. Claims 1 – 4 are objected to because of the following informalities: they encompass non-elected subject matter, specifically all molecules other than epinephrine. In the remarks filed 1 March 2005, applicant elected epinephrine for prosecution on the merits. Appropriate correction is required.

Rejections and Objections Withdrawn

5. The following rejections or objections made in the previous office action are withdrawn:

A) The objection to claims 3 – 5 is withdrawn in light of applicant's arguments filed 20 October 2005. Leptin is defined on p. 4 of the specification to include those elements recited in claims 3 and 4.

B) The rejection under 35 USC 112, second paragraph is withdrawn in light of the amendments.

Rejections and Objections Maintained

Claim Rejections - 35 USC § 112

6. Claims 1 – 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increased transport of leptin across the blood-brain barrier (BBB) following coadministration of leptin and intravenous or intraperitoneal epinephrine, cirazoline, benoxathian, phentolamine, yohimbine, prasozin, adenosine, or glutamate, does not reasonably provide enablement for increased transport of leptin across the BBB following administration by any other route of administration, or with any other compound, nor for co-administration of leptin variants, analogs, fusion proteins, derivates or fragments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is maintained for the reasons of record and explained in further detail herein. Applicant states, on p. 11 of the remarks filed 17 February 2006, that she presumes all previous rejections were withdrawn upon non-entry of the after-final amendment, since the advisory action did not explicitly reiterate every objection and rejection set forth in the previous office action. However, the after-final amendment was not entered and thus the amendments are arguments could not have been sufficient to overcome any rejections. Applicant did traverse the rejections under § 112, first paragraph in the remarks filed 20 October 2005, which have now been entered into the record.

On p. 12 of the remarks filed 20 October 2005, applicant cites *Johns Hopkins Univ. v Cellpro* in support of the argument that the claims are enabled. Applicant also argues, on p. 13 of the same remarks, that since at least one member of each recited genus is enabled, the claims are enabled generically. Applicant argues that all a skilled worker needs to do is repeat the method with another member of the same class. This clearly will not result in a successful method in most cases. For example, while tyrosine is marginally effective in enhancing leptin transport across the BBB, argenine, phenylalanine, tryptophan, leucine, threonine, and leucine have no effect on transport of leptin across the BBB (specification, p. 24). These amino acids all have a common structure, namely the presence of the amino group and the carboxyl group, linked by a carbon. However they all differ in the side-chain group. The only structural elements which are common to all members of the genus of amino acids, namely the carboxyl

and amino groups, are insufficient to increase transport of leptin across the BBB. The specification has set forth evidence of success with one member of the genus, but failure with many. The claims clearly are not enabled over the full scope of amino acids. The working examples and the guidance in the specification do not provide sufficient guidance to a skilled artisan to select those amino acids which would be expected to work in the method. Applicant argues, on p. 15 of the remarks filed 20 October 2005, that structure is not the only consideration to be considered, but rather that function must be considered as well. It is well-known in the art that amino acids all share some functions, namely that they are the building blocks of proteins. Here, however, there appears to be little or no correlation between a molecule's structure and its function. Epinephrine is able to increase transport across the BBB, but other molecular classes such as amino acids fail. Adrenergic agonists share common function in that they are all, by definition, able to augment or mimic the effects of adrenaline (a synonym for epinephrine) on the adrenergic receptor. However this function is not related to BBB transport of leptin. Amongst the adrenergic agonists tested by applicant ispoproterenol and arterenol are effective in this method, but neither clonidine nor L-phenylephrine are effective (specification, p. 26). If function, such as being able to mimic or stimulate the effects of adrenaline of its receptors, were sufficient to increase the transport of leptin across the BBB then one of skill in the art would expect that all the adrenergic agonists would increase said transport but half those tested are ineffective. The only example of a neurotransmitter that is not an amino acid modulating transport of leptin across the BBB is epinephrine. Thus it is not possible to generalize, either from a molecule's structure or from its known physiological functions, whether or how it will modulate transport of BBB.

Similarly, claim 2 recites many routes of administration. As set forth previously, some of these routes will work in the claimed method, and others will not. None of the compounds recited in claim 1 are effective when administered intracerebralventricularly (ICV; see p. 25). This is not a question of generalizing from guidance and prophetic examples in the specification, but rather is a statement of fact. If a skilled artisan were to select the route "intrathecal" from the group set forth in claim 2, it would be impossible to make the method work. The totality of the evidence set forth in the specification indicates administration of any agent by this route, even epinephrine, which is known to be effective when administered IV, always fails to increase leptin transport across the BBB. Applicant argues, on p. 18 of the remarks filed 20 October 2005, that

reference to ICV and intracisternal administration has been canceled, but these routes of delivery are clearly encompassed by "intrathecal" which is recited in claim 2.

Applicant again cites *Atlas Powder Co. v E.I. DuPont de Nemours & Co* and *In re Wands* as being supportive of the argument that some degree of experimentation is permissible, and that the quantity of experimentation can be large, if it is routine. Applicant also argues that a worker of ordinary skill in the art could take any compound and test to determine whether or not it increases the transport of leptin across the BBB. The examiner concedes that such testing is within the skill of the artisan. However the claimed invention is not a method of determining whether or not a test compound increases the transport of leptin across the BBB, but rather is a method of increasing such transport. The standard set forth in 35 USC § 112, first paragraph is not whether or not the specification provides sufficient description of the invention to enable a skilled artisan to begin experimentation related to the invention, but rather to "make and use" the claimed invention. The *Atlas* court ruled that when considering whether or not a claim is enabled commensurate with it scope,

> [I]f the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid. See, e.g., In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971)."

The examiner acknowledges that applicant has taught how to coadminister leptin with a broad range of compounds. The claims are drawn to methods of modulating the transport of leptin across the BBB and thus the consideration of whether the claims are enabled depends on whether the recited methods are sufficient to accomplish the goal recited in the preamble. In the instant case, there are so many non-enabled embodiments disclosed in the specification that the claims cannot be considered commensurate with their full scope.

Applicant argues, on p. 17 of the remarks filed 20 October 2005 that the interpretation of Fischer presented previously is taken straight from MPEP and thus provides supports the argument that the claims are enabled commensurate with their scope. The quotation provided reads "as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied" [emphasis added]. Here, the examples set forth in the specification do not meet that criterion, as they do not bear a reasonable correlation to the entire scope of the claim.

On p. 19 of the remarks filed 20 October 2005, that the claims are quite different from a single means claim. The examiner concedes that the claim is not a means-plus-function type claim as described in 35 USC 112, sixth paragraph. However, the claims are akin to single means claims as described in MPEP § 2164.08(a). As that section of the MPEP sets forth, claims which encompass every possible means of accomplishing something are subject to rejections under 35 USC § 112, first paragraph for unreasonable breadth when the specification discloses at most only those means known to the inventor. Here, the specification discloses a very few compounds suitable for accomplishing the method, but the claims encompass administration of "adrenergic agonists, adrenergic antagonists, neurotransmitters, cytokines, amino acids, opiate peptides, purinergic agonists, glutaminergic agonists and metabolites thereof" (see claim 1, from which all other claims depend). Thus while claim 1 is not actually a single means claim, the same logic that is set forth in MPEP § 2164.08(a) applies here.

For the reasons of record and explained in further detail above, the rejection under 35 USC 112, first paragraph, for lack of enablement commensurate in scope with the claims, stands.

7. Claims 1 – 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

This rejection is maintained for the reasons set forth previously and explained in further detail below. The claims are drawn to broad classes of agents which are not structurally limited. For example, claim 1 is drawn to neurotransmitters, which can be small molecules such as dopamine, single amino acids such as glutamate, or proteins such as neuropeptide Y. Similarly, the terms "agonists" and "antagonists" are functional, not structural definitions. As stated in the previous office action, certain embodiments that fall within the scope of leptin variants are described in the specification, although others such as "fragments" of leptin and "metabolites" of all agents do not meet the written description requirement. Claims 3 – 5 are very broad in that they are drawn to fragments of leptin, fragments of the analogs, fragments of the derivatives, and fragments of fusion proteins. The claims do not recite which parts of the sequence can be varied, which can be deleted, where insertions can be made, or even which parts of the

sequence must be present for the molecule to be considered "leptin". The instant disclosure of a handful of molecules, however, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. The examiner concedes that while compositions comprising those compounds recited in claim 1, part ii) are described in the art, the specification does not set forth a detailed description of those structural elements common to all members of the genera recited, which allows them to function in the claimed methods. The question is not merely whether the components recited in the claims have been described either in the specification or the prior art, but rather whether the specification provides evidence that applicant invented the claimed invention. See MPEP § 2163(I), and MPEP § 2163(I)(A), which states, in part:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function.

Here, applicant is claiming a method of modulating transport of leptin across the BBB, but has not set forth those structural elements common to all members of the compounds recited in claim 1 part ii) which impart the ability to modulate said transport.

Applicant is directed to the flow chart on p. 9 of the Revised Written Description Interim Guidelines Training Materials, available on the internet at <http://www.uspto.gov/web/offices/pac/writtendesc.pdf>, which is analogous to the instant situation. Claims 1 – 4 are genus claims because they encompass not just epinephrine, which has clearly been described as being able to modulate leptin transport, but also encompass methods of modulating transport by administration of many other broad classes of compounds which share no structure or function. Neither the art nor the specification discloses a representative number of species falling within the genus. There is not even identification of any particular structure that must be conserved for the method to successfully operate. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

The examiner concedes that leptin fragments and consensus leptins have sufficient support in the specification and prior art. However the term "chemically modified derivatives of leptin, and fragments thereof" is not adequately supported for the reasons of record. The specification does not provide evidence that applicant was in possession of the claimed invention. The invention as claimed is not the chemically modified derivative itself, but is a

method of transporting said structure across the BBB.

Claim Rejections - 35 USC § 103

8. Claims 1 – 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Banks et al. (1996. Peptides 17:305-311, cited on IDS) in view of Borges et al. (1994. Changes in brain microvessel endothelial cell monolayer permeability adrenergic drugs. European Journal of Pharmacology 269:243-248) and Caro et al. (The Lancet 348:159-161).

This rejection is maintained for the reasons of record. Applicant argues, beginning on p. 23 of the remarks filed 20 October 2005, that since epinephrine is a non-specific disruptor of the BBB, and since this non-specific disruption appears to be the mechanism under investigation by Borges, the teachings of Borges are not relevant. The examiner disagrees.

The actual mechanism which underlies the physiological process is immaterial as to the obviousness of the claimed invention. The newly-added limitation to claim 1 requires that the amount of epinephrine given be sufficient to modulate the transport of leptin across the BBB "through the specific leptin transporter of the blood brain barrier". The specification discloses that those doses of epinephrine which are effective to modulate the transport of leptin across the BBB are 40 nM – 200 nM of epinephrine (see p. 19). When 2 nM epinephrine is administered, the amount of ^{125}I-labeled leptin in the brain (as measured by the ratio of ^{125}I in the brain:blood; see right-hand column of the table on p. 19) is not significantly different from the amount of ^{125}I-labeled leptin in the brain after the control Ringer's solution is given. Clearly 2 nM epinephrine is not effective. At the other end of the scale, 400 nM epinephrine is not effective because it causes immediate death of all mice. The specification also provides evidence that 40 nM epinephrine increases leptin transport through a specific transporter, as labeled albumin does not enter the brain (see Table 3 beginning on p. 20). Thus the range of 40 – 200 nM epinephrine is the range that increases specific transport of leptin across the BBB.

The reference by Borges provides guidance as to the specific doses of epinephrine to be used. Figure 2 of the reference clearly shows that 0.1 uM (which is of course equivalent to 100 nM) and 1.0 uM of epinephrine are each effective in modulating blood-brain barrier permeability. Thus the reference directs the artisan of ordinary skill to administer either of these doses, or anywhere within the range defined by them, to modulate the permeability of the BBB. 100 nM is squarely within the range of doses demonstrated by applicant to be effective in modulating the specific leptin transporter. While the reference by Borges is silent as to whether or not the

specific leptin transporter is modulated by this dose, that is immaterial, as the reference provides guidance to select the same dose used by applicant.

Caro teaches the importance of increasing the transport of leptin across the BBB for treatment of obesity, as explained in more detail in the office action mailed 18 August 2005. Applicant argues, on p. 24 of the remarks filed 20 October 2005, that one of ordinary skill in the art would not look to Borges for a solution to the problem set forth by Caro, namely increasing leptin transport across the BBB, because the hypothesized physiological mechanisms in the two articles are different. The examiner disagrees. The reference by Borges shows that 100 nM of epinephrine is effective in modulating transport of large molecules across the BBB. The reference constitutes guidance to the artisan in selecting one of the doses shown by applicant to be effective in modulating the transport of leptin across the BBB via the specific leptin transporter.

Applicant argues, on p. 25 of the remarks filed 20 October 2005, that the reference by Borges teaches away from the claimed invention as epinephrine has some non-specific effects. Again, the examiner disagrees with the applicant's interpretation of both the data and the conclusions set forth in Borges. First, Borges does not conclude the specific mechanism by which epinephrine has its effects. Rather, Borges hypothesizes the existence of adrenergic receptors on brain capillary epithelial cells that form the BBB and says that "the mechanism of beta-adrenoceptors in these cells is less evident". The mere failure of Borges to measure the transport through specific as opposed to non-specific mechanisms does not constitute a teaching away. Nothing in Borges teaches the artisan of ordinary skill not to select a dose of 100 nM. Rather, the teachings directly guide the artisan to select this dose to modulate transport across the BBB and thus it is obvious to use it (see MPEP § 2144.05).

It would have been obvious to one of ordinary skill in the art to administer exogenous leptin and epinephrine in an amount effective to modulate transport of leptin across the BBB, with a reasonable expectation of success. The motivation to do so is to increase the amount of leptin that reaches the hypothalamus, thereby signaling satiety to obese patients. This motivation is provided by Caro. It would be reasonable to expect success, as Borges teaches that administration of epinephrine is sufficient to modulate transport of impermeable molecules across the BBB, and Banks teaches that leptin is an impermeable molecule because the transport system is saturable. Furthermore Borges provides guidance to select a dose of

epinephrine (100 nM) which has been shown in the instant disclosure to be effective in modulating transport of leptin across the BBB through its specific transporter.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
April 4, 2006

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER